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JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
CANELLA, KAREN A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No. 09/492,764	Applicant(s) JOVE ET AL.	
	Examiner Karen A Canella	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 19-32* is/are pending in the application.

4a) Of the above claim(s) *26,27,31 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,19-25 and 28-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/10/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicant's election with traverse of the peptide species in claim 25, namely SEQ ID NO:20, 22, 24, 25, 26, 27, 28, 30, 31, 32, 34, 35, 36, 37 and 38, over the species of claims 26 and 27, namely SEQ ID NO:12, 13, 14, 15, 16, 17, 18 and 19. The traversal is on the grounds that the Election of species is improper as it would not be undue burden to search for all the peptides of claims 25, 26 and 27. This has been considered but not found persuasive. Inclusion of all species of peptides would result in a search for 23 different peptides. Each of the peptides is a different product and must be searched separately in the databases and in the US Patent Shoes. Because the search for all of the peptides would not be co-extensive to the elected peptides of claim 25 therewould be undue burden on the examiner.

2. Claims 3-18 are canceled. Claims 1, 2 and 19-32 are pending. Claims 26, 27, 31 and 32, drawn to non-elected species, are withdawn from consideration. Claims 1, 19-25 and 28-30 are examined on the merits.

3. Acknowledgment is made of applicants priority claim to 60/117,600, filed January 27, 1999. However, upon review of the '600 application, support is found only for the STAT3 beta splice variant as an antagonist of STAT. Although the '600 application contemplates agents which selectively block STAT3 signaling in combination with conventional chemotherapy for more effective anti-tumor therapy, the disclosure of the STAT 3 beta splice variant in said '600 application does not provide adequate written description for the genus of antagonists claimed in the instant specification, nor the specific peptides of instant claims 25-27, 31 or 32. Further, the '600 application does not contemplate the inhibition of the SH2-pY interaction which is the subject matter of instant claims 23, 24, 27, 29 and 32. Accordingly, the instant claims will be given the effective priority date of the instant filing date of January 27, 2000.

4. The information disclosure statement (IDS) submitted on June 30, 2003 has been considered by the examiner. However, a 1449 form listing the references is not present in the case. Applicant is invited to provide a replacement 1449 form so that the examiner may provide an initialed and signed copy to applicant.

5. Claim 25 is objected to because the sequence listing identifies SEQ ID NO:32, 34 and 36 as identical to SEQ ID NO:20, 27 and 35, respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 19, 24 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19, 24 and 29 are vague and indefinite in the recitation of "SH2-pY interactions". It is unclear if said interaction refers to the interaction of the unphosphorylated SH2 domains of STAT with the phosphorylated receptor, or if this interaction refers to the interaction between the phosphorylated SH2 domains of STAT with other STAT molecules to form homo- or heterodimers, or if this interaction involves the binding of the tyrosine phosphorylated STAT to DNA. For purpose of examination, all alternatives will be considered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

Claim 20 is drawn to the method of claim 1, wherein said antagonist is an antibody. The STAT proteins are intracellular proteins without intracellular domains. In order for the method

of claim 1 to work, the antibody would have to be either taken up by the cell and transported to the appropriate intracellular compartment for interaction with STAT, or the antibody would have to be expressed intracellularly from a DNA construct to encode an intrabody. The specification provides no guidance as to how an antibody would be internalized into the target cell and directed or transported to the appropriate intracellular location to effect binding to STAT, thus one of skill in the art would not be able to carry out the instant method by administering an antibody as a protein. In order to make a construct encoding an intrabody, it is necessary to know at least the amino acid sequences of the paratopes of the anybody. the specification does not disclose a specific intrabody, by amino acid sequence or by means of a biological deposit, that would act to efficiently bind and inhibit STAT polypeptides intracellularly and thereby inhibit the growth of a tumor in vivo. In order to produce intrabodies the nucleic acid sequences, of minimally the complimentary determining region, are necessary (Jones et al., Advanced Drug Delivery Reviews 1998, page 154, column 1, lines 18 26, and page 160, lines 24 25). The specification clearly fails to describe the nucleic acid sequences of any antibody which would function as claimed. An intrabody by definition is an antibody that is expressed inside of a cell as a therapeutic agent. If the nucleic acid sequence encoding a antibody which is an antagonists of STAT was known, an efficient means of transferring the genes encoding said antibody to a person having a tumor would be necessary necessary. Even if the specification did disclose said nucleic acids the specification is not enabling for how to use antibody-encoding nucleic acids to treat tumors in a patient for the following reasons.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken

up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

Clearly, the specification fails to describe the necessary delivery vehicles for the insertion and expression of an intrabody. Thus without information such as the combination of CDR

sequences which form a surface which specifically binds STAT in a manner that prevents or decreases STAT binding to DNA, and further without specific guidance as to how to transfer genes encoding said antibody, one of skill in the art would be subject to undue experimentation in order to carry out said method .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 2, 19, 28, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable Han et al (Oncology Research, 1997, Vol. 9, pp. 581-587, reference of the IDS filed September 10, 2003) and Zushi et al (International Journal of Cancer, 1997, Vol. 78, pp. 326-330, reference of the IDS filed September 10, 2003) as evidenced by Ihle and Kerr (Trends in Genetics, 1995, Vol. 11, pp. 69-74).

Han et al teach that ethyl-2,5-dihydroxy cinnamate inhibited the tyrosine kinase activity of EGF receptor and its autophosphorylation. Han et al suggest that this compound be used in the treatment of human gliobastoma. Han et al do not specifically teach that said dihydroxy cinnamate antagonized STAT-DNA binding, however, it would be inherent in the action of the

dihydroxy cinnamate that STAT3 activation was inhibited because the phosphorylation of the EGF receptor is inhibited by said dihydroxy cinnamate. Zushi et al teach that another specific inhibitor EGF receptor, AG1478, effectively suppressed the activation of STAT3. Thus, without the autophosphorylation of the activated EGF receptor, STAT3 activation will not occur at said receptor in the presence of ethyl-2,5-dihydroxy cinnamate. Because STAT3 phosphorylation is inhibited, the dimerization of phosphorylated STAT3 is also inhibited as evidenced by Ihle and Kerr who teach that inhibition of the tyrosine phosphorylation of STAT inhibits dimerization of STAT (page 71, first column, forth paragraph). Therefore the inhibition of the phosphorylation of STAT3 by either ethyl-2,5-dihydroxy cinnamate or AG1478 also inhibits the dimerization of STAT , thus fulfilling the specific embodiment of claim 28 which specifies that the antagonist is an inhibitor of STAT dimerization. The teachings of Han et al and Zushi et al also fulfill the which also fulfills the specific embodiment of disrupting the normal SH2-pY interactions relative to the absence of the inhibitor, because in the presence of the inhibitor, dimerization of STAT3 will be inhibited due to lack of phosphorylation of STAT3, thus the SH2-pY interaction of dimerization will also be inhibited. Neither Han et al nor Zushi et al teach the administration of ethyl-2,5-dihydroxy cinnamate or AG1478 to a patient having cancer.

It would have been prima facie obvious at the time the invention was made to administer ethyl-2,5-dihydroxy cinnamate or AG1478 to patients with glioblastoma. One of skill in the art would have been motivated to do so by the suggestions of Han et al that the inhibition of EGF tyrosine kinase activity by ethyl-2,5-dihydroxy cinnamate be used as a method of treating glioblastoma. One of skill in the art would also recognize that AG1478 would also be active against glioblastoma because it is also inhibits the tyrosine kinase activity of the EGF receptor.

9. Claims 1, 2, 19, 28, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nielsen et al (PNAS, 1997, Vol. 94, pp. 6764-6769, reference of the IDS filed September 10, 2003) as evidenced by Ihle and Kerr (Trends in Genetics, 1995, Vol. 11, pp. 69-74).

Nielsen et al teach that AG490 inhibits the phosphorylation of STAT3 and the growth of mycosis fungoides tumor cells (page 6767 under the heading "Tryophostin AG490 Inhibits the Constitutive STAT3 Activation and Growth of MF Cells"). Ihle and Kerr teach that inhibition of the tyrosine phosphorylation of STAT inhibits dimerization of STAT (page 71, first column,

forth paragraph). Therefore the inhibition of the phosphorylation of STAT3 by AG490 also inhibits the dimerization of STAT , thus fulfilling the specific embodiment of claim 28 which specifies that the antagonist is an inhibitor of STAT dimerization. The teachings of Nielsen et al also fulfill the which also fulfills the specific embodiment of disrupting the normal SH2-pY interactions relative to the absence of the inhibitor, because in the presence of the inhibitor, dimerization of STAT3 will be inhibited due to lack of phosphorylation of STAT3, thus the SH2-pY interaction of dimerization will also be inhibited. Nielsen et al teach that abnormal Jak/STAT signaling contributes to the tumorigenesis of mycosis fungoides cells obtained from the affected skin of patients (abstract, last sentence). Nielsen et al do not specifically teach the administration of AG490 to a patient having mycosis fungoides (MF).

It would have been prima facie obvious at the time the claimed invention was made to administer AG490 to an MF patient. One of skill in the art would have been motivated to do so in order to disrupt the abnormal Jak/STAT signaling in the MF tumor cells and inhibit the growth of the MF tumor cells in vivo, as was taught by Nielsen et al in vitro.

10. Claims 1, 19, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Wasik et al (Leukemia and Lymphoma, 1998 Feb, Vol. 28, pp. 551-560) as evidenced by Ihle and Kerr (Trends in Genetics, 1995, Vol. 11, pp. 69-74).

The abstract of Wasik et al teaches that the compounds CT2576 and CT5589 inhibit the tyrosine phosphorylation of STAT5 (lines 14-16 of abstract). The abstract suggests that a potential role in the therapy of human T-cell lymphoma should be explored using said compounds (last sentence of abstract). Ihle and Kerr who teach that dimerization of STAT is inhibited by mutations of either the SH2 domain or the tyrosine phophorylation site (page 71, first column, forth paragraph), thus fulfilling the specific embodiment of claim 28 which specifies that the antagonist is an inhibitor of STAT dimerization. which also fulfills the specific embodiment of disrupting the normal SH2-pY interactions relative to the absence of the inhibitor, because in the presence of the inhibitor, dimerization of STAT5 will be inhibited, thus SH2-pY interactions relative to STAT5 will also be inhibited. The abstract of Wasik et al do not specifically teach the administration of CT2576 or CT5589 to patients having T-cell lymphoma.

It would have been prima facie obvious at the time the claimed invention was made to administer CT2576 or CT5589 to patients having T cell lymphoma. One of skill in the art would have been motivated by the suggestion of the abstract of Wasik et al to use said compounds in the treatment of patients. Further one of skill in the art would have been motivated to use CT2576 and CT5589 because they were relatively selective for inhibiting the tyrosine phosphorylation of STAT5 relative to other protein tyrosine kinases.

11. Claims 1, 2, 19, 21-25, 29 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Grigorieva et al (Blood, 1996, Vol. 88, No. 10, suppl. 1, part 1-2, page 104A) and the abstract of Yu et al (Journal of Immunology, 1997, Vol. 159, pp. 5206-5210) and the abstract of Sartor et al (Cancer Research, 1997, Vol. 57, pp. 978-987) and the abstract of Garcia et al (Cell Growth and Differentiation, 1997, Vol. 8, pp. 1267-1276) and Frank et al (Journal of Clinical Investigation, 1997, Vol. 100, pp. 3140-3148) in view of Fukada et al (Immunity, 1996, Vol. 5, pp. 449-460) and Caldenhoven et al (The Journal of Biological Chemistry, 1996, Vol.271, pp. 13221-1227) and Horvath et al (Genes and Development, 1995, Vol. 9, pp. 984-994) and Nakajia et al (EMBO, 1996, Vol. 15, pp. 3651-3658).

The abstract of Grigorieva et al (Blood, 1996, Vol. 88, No. 10, suppl. 1, part 1-2, page 104A) teaches that myeloma cells contained constitutively activated STAT3 in the nucleus independent of Il-6 stimulation.

The abstract of Yu et al (Journal of Immunology, 1997, Vol. 159, pp. 5206-5210) teaches that in T-lymphoma cells expressing the Lck tyrosine kinase, both the DNA binding and tyrosine phosphorylation of STAT3 and STAT5 is enhanced.

The abstract of Sartor et al (Cancer Research, 1997, Vol. 57, pp. 978-987) teaches that constitutively tyrosine-phosphorylated homodimers of STAT3 are present in breast cancer cell lines expressing EGF receptor.

The abstract of Garcia et al (Cell Growth and Differentiation, 1997, Vol. 8, pp. 1267-1276) teaches the constitutive activation of STAT3 in breast carcinoma cell lines versus normal breast epithelial cells. The abstract also teaches the activation of STAT3 by various viral oncogenes such as v-Fps, polyoma virus middle T antigen, v-Sis and v-Src. The abstract

concludes that activation of STAT3 is a common event during oncogenic transformations that directly or indirectly involve tyrosine kinase signaling pathways.

Frank et al (Journal of Clinical Investigation, 1997, Vol. 100, pp. 3140-3148) teach that constitutive tyrosine phosphorylation of STAT1 and STAT3 is observed in leukemic cells from patients with AML and ALL of both B and T-cell lineages (page 3142, first column, lines 4-9 and Table 1). Frank et al teach that in patients having CLL, STAT1 and STAT3 are constitutively phosphorylated on serine rather than tyrosine and suggest that the development of inhibitors of STAT serine kinases as a therapeutic strategy (page 3147, second column, lines 16-19).

Frank et al and the abstracts of Grigorieva et al, Yu et al , Sartor et al and Garcia et al teach the constitutive phosphorylation of STAT3 in transformed and cancerous cells. Neither the abstracts nor Frank teach the administration of a peptide which would bind to the SH2 domain of STAT3 or disrupt the interaction between the SH2-phosphotyrosine interaction as a therapeutic intervention against cancer.

Fukada et al (Immunity, 1996, Vol. 5, pp. 449-460) teach that the gp130 receptor activates STAT3 which transmits an anti-apoptotic signal by modulating the expression of Bcl-2 either directly or indirectly (page 453, second column, lines 3-7 and page 457, first column, lines 36-41).

Caldenhoven et al (The Journal of Biological Chemistry, 1996, Vol.271, pp. 13221-1227) teach that phosphorylation of the STAT proteins on tyrosine is required for dimerization, DNA-binding and the activation of transcription (page 13221, second column, lines 13-15). Caldenhoven et al teach that STAT3 beta, although able to bind to a pIRE site, is unable to activate a promoter comprising this pIRE site and that STAT3 beta is a strong dominant negative inhibitor of STAT3 (page 13222, first column, lines 4-9). Caldenhoven et al also teach that STAT1 beta, which is a splice variant of STAT1 alpha, is also unable to activate transcription, although phosphorylated on the appropriate tyrosine (page 13221, second column, lines 15-18). Caldenhoven et al teach that transcriptional activation by STAT3 is inhibited in the presence of STAT3 beta (page 13225, first column, lines 4-6). Caldenhoven et al suggest that the STAT3 beta exerts its dominant negative effect by either occupying the pIRE sites as a STAT3 beta homodimer by means of its greater affinity for the site, even in the presence of wild-type STAT3

which is more abundantly expressed, or by forming transcriptionally inactive heterodimers with the wild-type STAT proteins, or by both mechanisms together (page 13226, first column, last paragraph to second column, line 12). Thus, the teachings of Caldenhoven et al regarding the competitive inhibition of the pIRE site by the STAT3 dominant negative mutant fulfill the specific embodiment of claim 1 drawn to an antagonist of DNA binding; and the specific embodiments of claims 19 and 22-24 and 29 drawn to a peptide that binds to the SH2 domain of STAT3 and a peptide that disrupts the SH2-pY interaction. The STAT3beta is able to form heterodimers with wild type STAT3, and in so doing it is a peptide which binds to the SH2 domain of wild type STAT3. Further, forming heterodimers with wild-type STAT3 fulfills the specific embodiment of disrupting the SH2-pY interactions because tyrosine phosphorylated STAT3beta forms heterodimers with other phosphorylated STATS as evidenced by Ihle and Kerr who teach that dimerization of STAT is inhibited by mutations of either the SH2 domain or the tyrosine phophorylation site (page 71, first column, forth paragraph), which is consistent with tyrosine phosphorylated STATS, such as STAT3B, existing as dimers. Ihle and Kerr further teach that activated STATS can heterodimerize (page 72, first column, lines 10-11) fulfilling the specific embodiment of disrupting the normal SH2-pY interactions relative to the absence of STAT3B because STAT3B in a heterodimer with full length wild type STAT3 is a disruption in the SH2-pY interaction relative to the absence of STAT3B . The teachings of the STAT3B mutant also fulfill the specific embodiment of claim 25 as drawn to SEQ ID NO:20, 27, 31, 32, 34 and 37 because said SEQ ID NO are comprised within the STAT3B which comprises the first 715 residues of wild-type STAT3 (Caldenhoven et al, page 13222, second column, lines 17-19, under the heading "Isolation of a Short form of STAT3").

Horvath et al teach that the portion of STAT proteins which are responsible for STAT-specific DNA binding lie between residues 403-508 of STAT1 and 406-514 of STAT3 (page 990, lines 13-16). Horvath et al teach mutations in the sequence corresponding to residues 432-436 (VTEEL mutated to VTAAL) and residues 458-466 (SLPVVVISN mutated to SLPAAAISN) (page 990, first column, lines 6-14) cannot bind to DNA as well as the wild-type STAT3 (page 990-991, bridging sentence). Thus the teachings of Horvath et al fulfill the specific embodiment of claim 1 drawn to an antagonist of STAT DNA binding

Nakajia et al (EMBO, 1996, Vol. 15, pp. 3651-3658) teach that STAT3 mutants which do not bind to DNA could function as dominant negative STATs in a cytokine or receptor specific manner (page 3652, first column, lines 9-14 and 19-22 under the heading "STAT proteins with mutations…"). Nakajia et al et al teach that the result obtained by experimentation are consistent with mutants in which residues important for DNA binding were mutated inhibit the DNA binding activity of STAT dimers comprising the wild-type STAT and the DNA-binding defective STAT mutant (page 3655, first column, lines 18-19). Thus the teachings of Nakajia et al fulfill the specific embodiment of claim 1 drawn to an antagonist of STAT DNA binding, as well as the limitations of claims 19 and 24, specifying the disruption of the SH2-pY interactions, because the non-DNA-binding mutants formed heterodimers with the wild type STAT, thus disrupting the normal SH2-pY interactions relative to the absence of said mutant. The teachings of Nakajia et al also fulfilled the specific embodiments of claim 22 drawn to a peptide that binds the SH2 domain of STAT3, because the mutant STAT3 in a heterodimer with wild type STAT3 would binds to the SH2 domain of STAT3.

It would have been prima facie obvious at the time the claimed invention was made to administer a STAT3 mutant that was defective in DNA binding or which decreased the transcriptional activation by STAT3 by binding to wild-type STAT3. One of skill in the art would have been motivated to do so by the teachings of Caldenhoven et al on the properties of STAT3B; the teachings of Horvath et al and Nakajia et al on the properties of STAT3 mutants which are deficient in DNA binding; the teachings of Frank et al and the abstracts of Grigorieva et al, Yu et al , Sartor et al and Garcia et al on the constitutive phosphorylation of STAT3 in transformed and cancerous cells, and particularly the suggestion of Frank et al on the development of inhibitors of STAT serine kinases as a therapeutic strategy for the treatment of CLL which exhibits constitutive serine phosphorylation: One of skill in the art would reasonably conclude that inhibitors of STAT tyrosine kinases would also be a therapeutic strategy for the treatment of AML and ALL wherein STAT3 is constitutively activated by tyrosine phosphorylation. One of skill in the art would understand that dominant negative STAT3 which was deficient or inefficient at DNA binding would overcome the constitutive activation of STAT3. One of skill in the art would also be motivated to disrupt the anti-apoptotic signal

generated from constitutive activation of STAT3 as taught by Fukada et al so that the cancerous cells would not be resistant to apoptosis.

12. Claims 1, 2, 19, 21, 24, 25 and 28-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Grigorieva et al (Blood, 1996, Vol. 88, No. 10, suppl. 1, part 1-2, page 104A) and the abstract of Yu et al (Journal of Immunology, 1997, Vol. 159, pp. 5206-5210) and the abstract of Sartor et al (Cancer Research, 1997, Vol. 57, pp. 978-987) and the abstract of Garcia et al (Cell Growth and differentiation, 1997, Vol. 8, pp. 1267-1276) and Frank et al (Journal of clinical Investigation, 1997, Vol. 100, pp. 3140-3148) in view of Fukada et al (Immunity, 1996, Vol. 5, pp. 449-460) and Zushi et al (International Journal of Cancer, 1997, Vol. 78, pp. 326-330, reference of the IDS filed September 10, 2003) and Horvath et al (Genes and Development, 1995, Vol. 9, pp. 984-994).

The abstract of Grigorieva et al (Blood, 1996, Vol. 88, No. 10, suppl. 1, part 1-2, page 104A) teaches that myeloma cells contained constitutively activated STAT3 in the nucleus independent of Il-6 stimulation.

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The abstract of Garcia et al (Cell Growth and differentiation, 1997, Vol. 8, pp. 1267-1276) teaches the constitutive activation of STAT3 in breast carcinoma cell lines versus normal breast epithelial cells. The abstract also teaches the activation of STAT3 by various viral oncogenes such as v-Fps, polyoma virus middle T antigen, v-Sis and v-Src. The abstract concludes that activation of STAT3 is a common event during oncogenic transformations that directly or indirectly involve tyrosine kinase signaling pathways.

Frank et al (Journal of clinical Investigation, 1997, Vol. 100, pp. 3140-3148) teach that constitutive tyrosine phosphorylation of STAT1 and STAT3 is observed in leukemic cells from patients with AML and ALL of both B and T-cell lineages (page 3142, first column, lines 4-9

and Table 1). Frank et al teach that in patients having CLL, STAT1 and STAT3 are constitutively phosphorylated on serine rather than tyrosine and suggest that the development of inhibitors of STAT serine kinases as a therapeutic strategy (page 3147, second column, lines 16-19).

The abstracts and Frank et al teach the constitutive phosphorylation of STAT3 in transformed and cancerous cells. Neither the abstracts nor Frank teach the administration of a peptide which would bind to the SH2 domain of STAT3 or disrupt the interaction between the SH2-phosphotyrosine interaction as a therapeutic intervention against cancer.

Fukada et al (Immunity, 1996, Vol. 5, pp. 449-460) teach that any one of the four tyrosines in the carboxyl terminus of the gp130 receptor can induce tyrosine phosphorylation and activation of STAT3, but that the phosphorylation of the third tyrosine is critical for cell survival (page 453, second column, lines 3-7). Fukada et al teach that expression of dominant negative STAT3 mutants in which Tyr705 was mutated to Ala (STAT3F), and Glu434 and Glu435 were mutated to Ala (STAT3D) caused cells to undergo apoptosis (page 453, second column, lines 14-30). Fukada et al teach that STAT3 transmits an anti-apoptotic signal by modulating the expression of Bcl-2 either directly or indirectly (page 457, first column, lines 36-41). The teachings of Fukada et al fulfill the specific embodiments of claims 19, 24 and 29 specifying that the antagonist inhibits SH2-pY interaction, and claim 28 specifying that the antagonist inhibits STAT dimerization as evidenced by Ihle and Kerr who teach that dimerization of STAT is inhibited by mutations of the tyrosine phophorylation site (page 71, first column, forth paragraph). The teachings of Fukada et al also fulfill the specific embodiments of claim 25 drawn to claims 20, 27, 31, 32, 34 and 37 because SEQ ID NO: 20, 27, 32, 34 and 37 are comprised within the STAT3F and SEQ ID NO:31 is comprised within the STAT3D mutants.

Zushi et al (International Journal of Cancer, 1997, Vol. 78, pp. 326-330, reference of the IDS filed September 10, 2003) teach that in oncogenic Ras-transfected intestinal epithelial cells, the constitutive activation of STAT3 is dependent upon an EGF-related growth factor loop (page 329, second column, lines 5-10 of the last paragraph). Zushi et al teach that expression of the ani-apoptotic proteins Bcl-2 and Bcl-xL are regulated by activated STAT3 (page 329, second column, lines 1-20) and that expression of a construct encoding a dominant-negative STAT3

(Y705F) caused apoptotic cell death (page 328, second column, lines 2-6), thus disrupting the autocrine loop responsible for STAT3 activation.

Horvath et al (Genes and Development, 1995, Vol. 9, pp. 984-994) teach that mutation of the STAT3 protein at tyrosine 705 blocks the phosphorylation and subsequent activation as a DNA-binding protein (page 987,second column, lines 8-11 and lines 18-20, under the heading "Localization of specific DNA-binding region of STAT proteins". Thus the teachings of Horvath et al fulfill the specific embodiment of claim 1 drawn to an antagonist of STAT DNA binding. Further the teachings of Horvath et al fulfill the specific embodiments of claims 19 and 24 as evidenced by Nakajia et al (EMBO, 1996, Vol. 15, pp. 3651-3658) who teach that STAT3 mutants carrying either a phenylalanine substituted for tyrosine at position 705 are consistent with said mutants competing with endogenous STAT proteins for recruitment to the activated receptor or receptor-kinase complexes (page 3655, first column, lines 14-17 under the heading "Discussion"). Thus, the teachings of Horvath et al fulfill the specific embodiment of claims 19 and 24, specifying the disruption of the SH2-pY interactions as interaction of the SH2 domain with the activated receptor is necessary for phosphorylation and activation of STAT3. The teachings of Horvath et al also fulfill the specific embodiments of claim 28 which specify that the antagonist is an inhibitor of STAT dimerization as evidenced by Ihle and Kerr who teach that dimerization of STAT is inhibited by mutations of either the SH2 domain or the tyrosine phophorylation site (page 71, first column, forth paragraph).

It would have been prima facie obvious at the time the claimed invention was made to administer a STAT3 mutant that was defective in tyrosine phosphorylation relative to wild-type STAT3. One of skill in the art would have been motivated to do so by the teachings of Zushi et al and Horvath et al on the properties of a Y705 STAT3 mutant; the teachings of Frank et al and the abstracts of Grigorieva et al, Yu et al , Sartor et al and Garcia et al on the constitutive phosphorylation of STAT3 in transformed and cancerous cells, and particularly the suggestion of Frank et al on the development of inhibitors of STAT serine kinases as a therapeutic strategy for the treatment of CLL which exhibits constitutive serine phosphorylation: One of skill in the art would reasonably conclude that inhibitors of STAT tyrosine kinases would also be a therapeutic strategy for the treatment of AML and ALL wherein STAT3 is constitutively activated by tyrosine phosphorylation. One of skill in the art would understand that dominant negative

STAT3 which was unable to become phosphorylated would be recruited to the activated receptor, but would not serve as a second messenger, and therefore disrupt the autocrine loop responsible for the constitutive activation of STAT3 as taught by Zushi et al .

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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Karen A. Canella, Ph.D.
06/01/2004

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER